United States General Accounting Office

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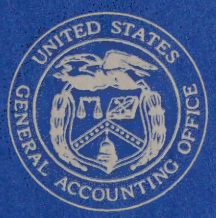
Report to Congressional Requesters

April 1999

ANTIMICROBIAL RESISTANCE

Data to Assess Public Health Threat From Resistant Bacteria Are Limited



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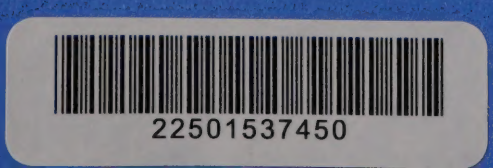

GAO

United States
General Accounting Office
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Health, Education, and
Human Services Division

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April 28, 1999

The Honorable Edward M. Kennedy
Ranking Minority Member
Committee on Health, Education,
Labor, and Pensions
United States Senate

The Honorable Tom Harkin
Ranking Minority Member
Committee on Agriculture,
Nutrition, and Forestry
United States Senate

The *Staphylococcus aureus* bacterium (*S. aureus*)—one of the most common causes of infections worldwide—has long been considered treatable with antimicrobial drugs. Recently, however, a number of *S. aureus* infections were found that resisted most available antimicrobials—including vancomycin, the last line of treatment for these and some other infections. For example, several years ago in Japan, a 4-month-old infant who had developed an *S. aureus* infection following surgery died after a month of treatments with various antimicrobials, including vancomycin. About a year later, three elderly patients in the United States with multiple chronic conditions were infected with this type of *S. aureus*—now known as vancomycin intermediate-resistant *Staphylococcus aureus* (VISA). They were treated with numerous antimicrobials for an extended period of time and eventually died, but it is unclear what role VISA played in their deaths. More recently, a middle-aged cancer patient in Hong Kong was admitted to a hospital with a fever and died despite 2 weeks of treatment for VISA.

Cases like these have heightened concern about antimicrobial resistance. To better understand the potential threat to the public's health, you asked us to (1) summarize what is known about the current public health burden—in terms of illnesses, deaths, and treatment costs—due to antimicrobial resistance; (2) assess the potential future burden, given what is known about the development of resistance in microbes and usage of antimicrobials; and (3) describe federal efforts to gather and provide information about resistance. Although resistance has been observed in many kinds of microbes—including bacteria, viruses, parasites, and fungi—the scope of this report, the first in a series you have requested, is limited to bacteria. To conduct our work, we reviewed scientific and

medical literature and spoke with experts in government agencies as well as in academia and private industry. We conducted our work between June 1998 and April 1999 in accordance with generally accepted government auditing standards. (For more information about our scope and methodology, see app. I.)

Results in Brief

Although many studies have documented cases of infections that are difficult to treat because they are caused by resistant bacteria, the full extent of the problem remains unknown. More specifically, we found many sources of information about the public health burden in the United States attributable to resistant bacteria, but each source has limitations and provides data on only part of the burden. For example, the public health burden attributable to resistant tuberculosis (TB) and gonorrhea is relatively well characterized because nationwide surveillance systems monitor these diseases. However, little is known about the extent of most other diseases that can be caused by resistant bacteria, such as otitis media (middle ear infection), gastric ulcers, and cystitis (inflammation of the bladder) because they are not similarly monitored.

The development and spread of resistant bacteria worldwide and the widespread use of various antibacterials create the potential for the U.S. public health burden to increase. Data indicate that resistant bacteria are emerging around the world, that more kinds of bacteria are becoming resistant, and that bacteria are becoming resistant to multiple drugs. While little information is publicly available about the actual quantities of antibacterials produced, used, and present in the environment, it is known that antibacterials are used extensively around the world in human and veterinary medicine, in agricultural production, and in industrial and household products and that they have been found in food, soil, and water.

A number of federal agencies and international organizations that receive U.S. funds collect information about different aspects of antibacterial resistance, and some ongoing efforts involve collaboration among agencies. For example, the Centers for Disease Control and Prevention (CDC) is the primary source of information about the number of infections caused by resistant bacteria. CDC also collects information on resistance found in bacterial samples and the use of antibacterial drugs in human medicine. The U.S. Department of Agriculture (USDA) collects information about resistant bacteria in animals and antibacterial drug residues in food. The Food and Drug Administration (FDA) also has a program to monitor antibacterial residues in food. CDC, USDA, and FDA are collaborating on

efforts to monitor resistant bacteria that can contaminate the food supply. The Department of Defense conducts surveillance for antibacterial resistance at 13 military sites in the United States and at its 6 tropical overseas laboratories. Internationally, the World Health Organization serves as a clearinghouse for data on resistance in bacteria isolated from people and animals from many different countries. Over the next several years, ongoing efforts to improve existing data sources and to create new ones may allow better characterization of the public health burden. Moreover, several agencies have data or access to data that, although not originally intended for these purposes, could be used to learn more about the number of resistant infections, treatment costs, and antibacterial usage.

Background

Bacteria exist almost everywhere—in water, soil, plants, animals, and humans. Bacteria can transfer from person to person, among animals and people, from animals to animals, and through water and the food chain. Most bacteria do little or no harm, and some are even useful to humans. However, others are capable of causing disease. Moreover, the same bacteria can have different effects on different parts of the host body. For example, *S. aureus* on the skin can be harmless, but when they enter the bloodstream through a wound they can cause disease.

An antibacterial is anything that can kill or inhibit the growth of bacteria, such as high heat or radiation or a chemical. Antibacterial chemicals can be grouped into three broad categories: antibacterial drugs, antiseptics, and disinfectants. Antibacterial drugs are used in relatively low concentrations in or upon the bodies of organisms to prevent or treat specific bacterial diseases without harming the organism. They are also used in agriculture to enhance the growth of food animals.[1] Unlike antibacterial drugs, antiseptics and disinfectants are usually nonspecific with respect to their targets—they kill or inhibit a variety of microbes. Antiseptics are used topically in or on living tissue, and disinfectants are used on objects or in water. (For more information on resistant bacteria, see app. II; for more on antibacterial use, see app. III.)

Antibacterial resistance describes a feature of some bacteria that enables them to avoid the effects of antibacterial agents. Bacteria may possess characteristics that allow them to survive a sudden change in climate, the effects of ultraviolet light from the sun, or the presence of an antibacterial

[1]For more information on the use of antibacterial drugs in animal feed, see Food Safety: The Agricultural Use of Antibiotics and Its Implications for Human Health (GAO/RCED-99-74, Apr. 28, 1999).

chemical in their environment. Some bacteria are naturally resistant. Other bacteria acquire resistance to antibacterials to which they once were susceptible.

The development of resistance to an antibacterial is complex. Susceptible bacteria can become resistant by acquiring resistance genes from other bacteria or through mutations in their own genetic material (DNA). Once acquired, the resistance characteristic is passed on to future generations and sometimes to other bacterial species.

Antibacterials have been shown to promote antibacterial resistance in at least three ways: through (1) encouraging the exchange of resistant genes between bacteria, (2) favoring the survival of the resistant bacteria in a mixed population of resistant and susceptible bacteria, and (3) making people and animals more vulnerable to resistant infection.[2] Although the contribution of antibacterials in promoting resistance has most often been documented for antibacterial drugs, there are also reports of disinfectant use contributing to resistance and concerns about the potential for antiseptics to promote resistance. For example, in the case of disinfectants, researchers have found that chlorinated river water contains more bacteria that are resistant to streptomycin than does nonchlorinated river water.[3] Also, it has been shown that some kinds of *Escherichia coli (E. coli)* resist triclosan—an antiseptic used in a variety of products, including soaps and toothpaste.[4] This raises the possibility that antiseptic use could contribute to the emergence of resistant bacteria.

While antibacterials are a major factor in the development of resistance, many other factors are also involved—including the nature of the specific bacteria and antibacterial involved, the way the antibacterial is used, characteristics of the host, and environmental factors. Therefore, the use of antibacterials does not always lead to resistance.

[2]See, for example, (1) F. Doucet-Populaire and others, "Inducible Transfer of Conjugative Transposon Tn*1545* from *Enterococcus faecalis* to *Listeria moncytogenes* in the Digestive Tracts of Gnotobiotic Mice," Antimicrobial Agents and Chemotherapy, Vol. 35 (1991), pp. 185-87; (2) V. L. Yu and others, "Patient Factors Contributing to the Emergence of Gentamicin-Resistant *Serratia marcescens*," The American Journal of Medicine, Vol. 66 (1979), pp. 468-72; and (3) R. P. Mouton and others, "Correlations Between Consumption of Antibiotics and Methicillin Resistance in Coagulase Negative Staphylococci," Journal of Antimicrobial Chemotherapy, Vol. 26 (1990), pp. 573-83.

[3]J. L. Armstrong and others, "Selection of Antibiotic-Resistant Standard Plate Count Bacteria During Water Treatment," Applied and Environmental Microbiology, Vol. 44 (1982), pp. 308-16.

[4]L. M. McMurry and others, "Triclosan Targets Lipid Synthesis," Nature, Vol. 394 (1998), pp. 531-32.

Data Insufficient to Determine Full Extent of Public Health Burden Associated With Antibacterial Resistance

Although we found many sources of information about the public health burden in the United States attributable to resistant bacteria, each source provides data on only part of the burden. Specifically, we found information about resistant diseases that result in hospitalization or are acquired in the hospital and information about two specific diseases—TB and gonorrhea. Moreover, no systematic information is available about deaths from diseases caused by resistant bacteria or about the costs of treating resistant disease. Consequently, the overall extent of disease, death, and treatment costs resulting from resistant bacteria is unknown.

Estimates From Hospital Data

The primary source of information on cases of disease caused by resistant bacteria is the National Hospital Discharge Survey (NHDS)—conducted annually by CDC's National Center for Health Statistics (NCHS).[5] It estimates drug-resistant infections among hospitalized patients, including both patients with a resistant infection that caused them to be hospitalized and patients who acquired a resistant infection while in the hospital for another reason. According to this survey, in 1997, hospitals discharged 43,000 patients who had been diagnosed with and treated for infections from drug-resistant bacteria. (See table 1.)

Table 1: Estimated Number of Yearly Short-Stay Hospital Discharges Listing Infection With Drug-Resistant Bacteria Among Diagnoses, 1994 Through 1997

	1994	1995	1996	1997[a]
Number of discharges	11,000	18,000	22,000	43,000

[a]Data for 1997 are unpublished.

Source: CDC, NCHS, National Hospital Discharge Survey.

These numbers, however, should be interpreted cautiously. The survey's diagnostic codes for designating infections with drug-resistant bacteria are, in most cases, not required for reimbursement, and they went into effect only in October 1993—though the survey has been conducted since 1965. Therefore, estimating the number of cases of infections with drug-resistant bacteria based on these codes likely results in an underestimate. In addition, increases in the number of discharged patients who had been treated for infections from drug-resistant bacteria may reflect an increase in the use of the new codes and not an actual increase in the incidence of resistant infections.

[5]E. J. Graves and L. J. Kozak, "Detailed Diagnoses and Procedures, National Hospital Discharge Survey, 1996," Vital and Health Statistics, Series 13, No. 138 (NCHS, 1998).

Data on five predominant bacterial infections acquired in hospitals from CDC's Hospital Infections Program further suggest that the estimates derived from NHDS may be too low. Since the discharge survey is not limited to specific infections and includes diseases acquired outside the hospital, it would be expected that estimates derived from the survey would be greater. However, estimates from the Hospital Infections Program indicate that the number of resistant infections acquired in hospitals is many times greater. (See table 2.)

Table 2: Estimated Number of Hospital-Acquired Infections Caused by Selected Resistant Bacteria in the United States in 1995

Resistant Bacteria	Cases
Methicillin-resistant *S. aureus*	70,000
Methicillin-resistant coagulase-negative *Staphylococcus*	121,000
Vancomycin-resistant *Enterococcus*	14,000
Ceftazidime-resistant *Pseudomonas aeruginosa*	10,000
Ampicillin-resistant *E. coli*	64,000
Total	**279,000**

Source: CDC, Hospital Infections Program, unpublished extrapolation from the National Nosocomial Infections Surveillance system.

These estimates should also be interpreted cautiously. CDC estimated the number of cases for each type of resistant bacteria by extrapolating from data on the 276 hospitals participating in CDC's National Nosocomial Infections Surveillance (NNIS) system to all hospitals in the United States. NNIS hospitals, however, are not representative of all hospitals; they are disproportionately large, urban, and affiliated with medical schools, and therefore likely to have more severely ill patients. Moreover, unlike NHDS, which surveys discharge codes that denote actual infections, the NNIS hospitals test bacterial samples in laboratories and thus may be detecting resistant bacteria that did not necessarily result in a patient treated for infection. Consequently, these CDC extrapolations probably overestimate the number of cases of these types of resistant bacterial disease.

Data From Surveillance of Disease

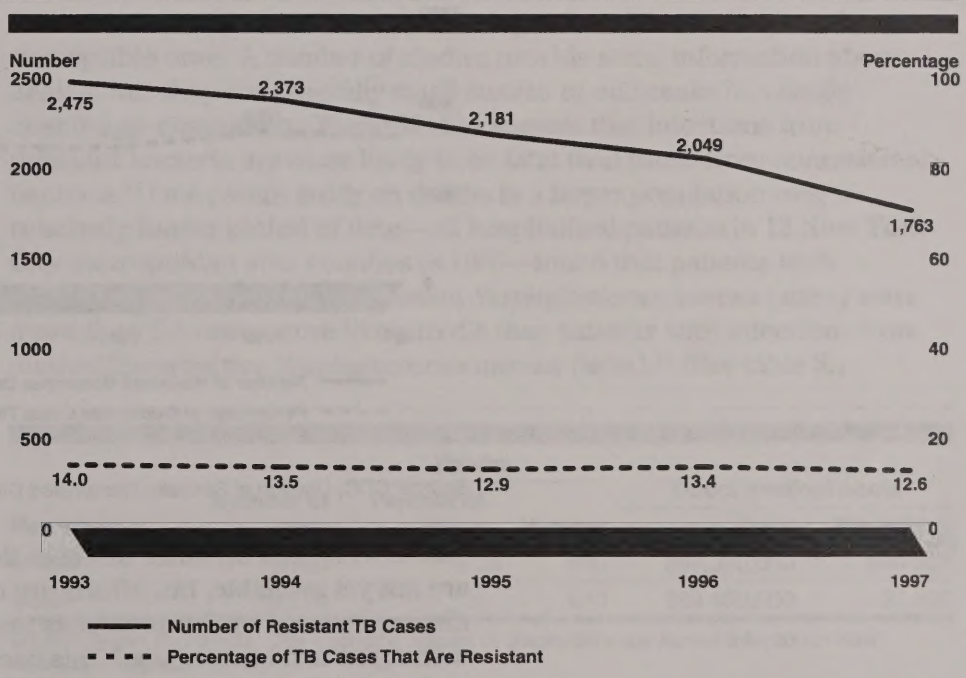
Another source of information on cases of disease caused by resistant bacteria is data developed through surveillance of infectious diseases. However, nationwide data on such diseases are currently limited to TB and gonorrhea.

Tuberculosis

CDC's Division of Tuberculosis Elimination collects reports of all verified TB cases from states. TB is an infectious disease, most commonly of the

lungs, caused by *Mycobacterium tuberculosis*. In response to increased incidence of TB in the late 1980s and early 1990s, CDC, in conjunction with state and local health departments, expanded national surveillance to include tests for resistance for all confirmed cases reported in 1993 and later. In 1997, the most recent year for which data have been published, tests were performed on 88.5 percent of confirmed TB cases reported in the United States.[6] Of these, 12.6 percent were resistant to at least one antituberculosis drug. Although the number of cases of TB has declined, the proportion of cases that are resistant has remained relatively stable (see fig. 1).

Figure 1: Number and Percentage of Tuberculosis Patients Infected With Resistant Bacteria, by Year of Case Report



Source: CDC, Division of Tuberculosis Elimination.

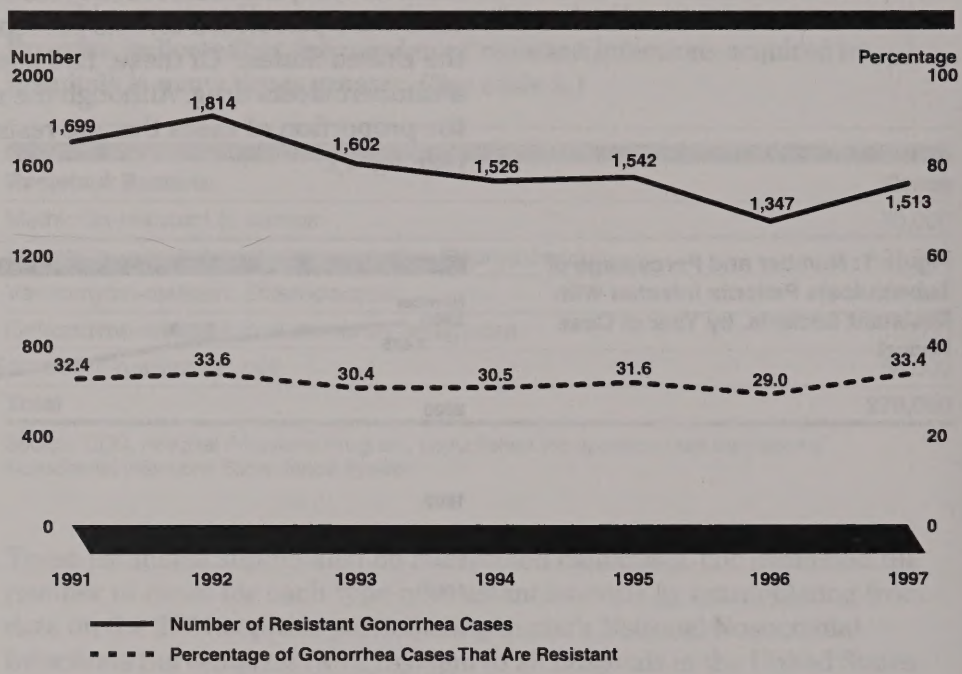
Gonorrhea

Through its Division of Sexually Transmitted Disease Prevention, CDC also conducts nationwide surveillance of gonorrhea, which is caused by the bacterium *Neisseria gonorrhoea*. CDC supplements nationwide surveillance of gonorrhea infections with a Gonococcal Isolate Surveillance Project (GISP), a network consisting of clinics in 27 cities. In 1997, 33.4 percent of the gonococcal samples collected by GISP were

[6]CDC, "Reported Tuberculosis in the United States, 1997" (Atlanta, Ga.: July 1998).

resistant to penicillin, or tetracycline, or both.[7] Figure 2 shows that the proportion of gonorrhea resistant to these drugs has remained relatively stable since 1991.

Figure 2: Number and Percentage of Gonorrhea Patients Infected With Resistant Bacteria in GISP Cities, by Year of Case Report



Source: CDC, Division of Sexually Transmitted Disease Prevention.

Other Diseases

Nationwide data on other diseases that can be caused by resistant bacteria are not yet available, but efforts are under way to monitor invasive diseases caused by *Streptococcus pneumoniae* (*S. pneumoniae*), including meningitis and bacteremia.[8] This bacterium was once routinely treatable with penicillin; however, since the mid-1980s, penicillin resistance has emerged, and some infections are susceptible only to vancomycin. In 1995, resistant *S. pneumoniae* was designated as a nationally reportable disease, and by 1998, 37 states were conducting public health surveillance on this bacterium.[9]

[7]CDC, "Sexually Transmitted Disease Surveillance, 1997" (Atlanta, Ga.: Sept. 1998).

[8]Meningitis is inflammation of the membranes surrounding the brain or spinal cord; bacteremia is an infection of the blood.

[9]Emerging Infectious Diseases: Consensus on Needed Laboratory Capacity Could Strengthen Surveillance (GAO/HEHS-99-26, Feb. 5, 1999).

We found no efforts yet under way to collect systematic information on bacterial resistance in other diseases that have exhibited resistance to the antibacterial drugs usually used to treat them. Many common diseases caused by bacteria that have exhibited resistance—such as otitis media, gastric ulcers, cystitis, and strep throat—are typically acquired outside the hospital. In addition, they typically do not result in hospitalization, are often treated without laboratory identification of the underlying cause, and are not notifiable. Thus, they are not reflected in existing data sources.

Deaths and Treatment Costs

The number of deaths caused by resistant bacteria cannot be determined because the standard source of data on deaths—vital statistics compiled from death certificates—does not distinguish resistant infections from susceptible ones. A number of studies provide some information about deaths, but they are generally small studies of outbreaks in a single hospital or community. These studies suggest that infections from resistant bacteria are more likely to be fatal than those from nonresistant bacteria.[10] One recent study on deaths in a larger population over a relatively longer period of time—all hospitalized patients in 13 New York City metropolitan area counties in 1995—found that patients with infections from methicillin-resistant *Staphylococcus aureus* (MRSA) were more than 2.5 times more likely to die than patients with infections from methicillin-sensitive *Staphylococcus aureus* (MSSA).[11] (See table 3.)

Table 3: Cases, Deaths, and Treatment Costs of Patients Infected With S. aureus in Metropolitan New York City Hospitals in 1995, by Resistance Category

		Deaths		Direct medical costs	
Resistance	Number of cases	Percent of cases	Number	Total	Per patient
MRSA	2,780	21%	590	$94,500,000	$34,000
MSSA	10,770	8	810	339,400,000	31,500

Source: Rubin and others, "The Economic Impact of *Staphylococcus aureus* Infection in New York City Hospitals," p. 14.

Because the number of cases of resistant disease is not known and the average treatment cost of cases is not available, we are unable to estimate the overall cost of treating drug-resistant bacterial disease. Although information about the cost of treating infections caused by resistant bacteria is limited, it suggests that resistant infections are generally more

[10]S. D. Holmberg and others, "Health and Economic Impacts of Antimicrobial Resistance," Reviews of Infectious Diseases, Vol. 9, No. 6 (1987), pp. 1065-78.

[11]R. J. Rubin and others, "The Economic Impact of *Staphylococcus aureus* Infection in New York City Hospitals," Emerging Infectious Diseases, Vol. 5, No. 1 (1999), pp. 9-17.

costly to treat than those caused by susceptible bacteria.[12] For example, in the study of the impact of *S. aureus* infections in metropolitan New York City hospitals, direct medical costs—consisting of hospital charges, professional fees during hospitalization, and medical services after discharge—were 8 percent higher for a patient with MRSA than for a patient with MSSA. The higher cost of treating MRSA infections reflects the higher cost of vancomycin use, longer hospital stay, and patient isolation procedures. Similarly, a study of the cost of treating TB, based on a survey of five programs—in Alabama; Illinois; New Jersey; Texas; and Los Angeles, California—showed that outpatient therapy costs for multidrug-resistant TB were more than 3 times as great as for susceptible TB.[13] (See table 4.) Appendix IV describes other studies of the cost of treating resistant disease.

Table 4: Expenditures in 1991 for Outpatient TB Therapy, by Patient Type

Patient type	Cost per patient
Susceptible TB	$2,300
Single-drug-resistant TB	5,000
Multidrug-resistant TB	8,000

Source: Brown and others, "Health-Care Expenditures for Tuberculosis in the United States," p. 1598.

Increasing Resistance and Widespread Antibacterial Use Could Increase Public Health Burden

Existing data on resistant bacteria, which can cause infections, and antibacterial use, which can promote the development of resistance, provide clues for understanding how the future U.S. public health burden could develop. Because resistant bacteria from anywhere in the world could result in an infection in the United States, the development of resistance globally must also be considered.[14] The data available suggest that antibacterial resistance is increasing worldwide and that antibacterial agents are used extensively. Consequently, the U.S. public health burden could increase.

[12]Holmberg and others, "Health and Economic Impacts of Antimicrobial Resistance," and L. A. Lee and others, "Increase in Antimicrobial-Resistant *Salmonella* Infections in the United States, 1989-1990," Journal of Infectious Diseases, Vol. 170, No. 1 (1994), pp. 128-34.

[13]R. E. Brown and others, "Health-Care Expenditures for Tuberculosis in the United States," Archives of Internal Medicine, Vol. 155, No. 15 (1995), pp. 1595-1600.

[14]The transport of resistant bacteria by people, animals, and products creates the opportunity for such bacteria to enter the United States and contribute to an increase in the public health burden. Each year, tens of millions of travelers enter and depart from the United States, and in 1997, over 9 billion kilograms of fruits and vegetables in this country were imported.

Available Data Indicate That Antibacterial Resistance Is Increasing

Without routine testing and systematic data collection globally, the prevalence of resistant bacteria worldwide cannot be determined. Data from laboratories that monitor for resistant bacteria, however, show that resistance in human and animal bacteria is increasing in four ways.

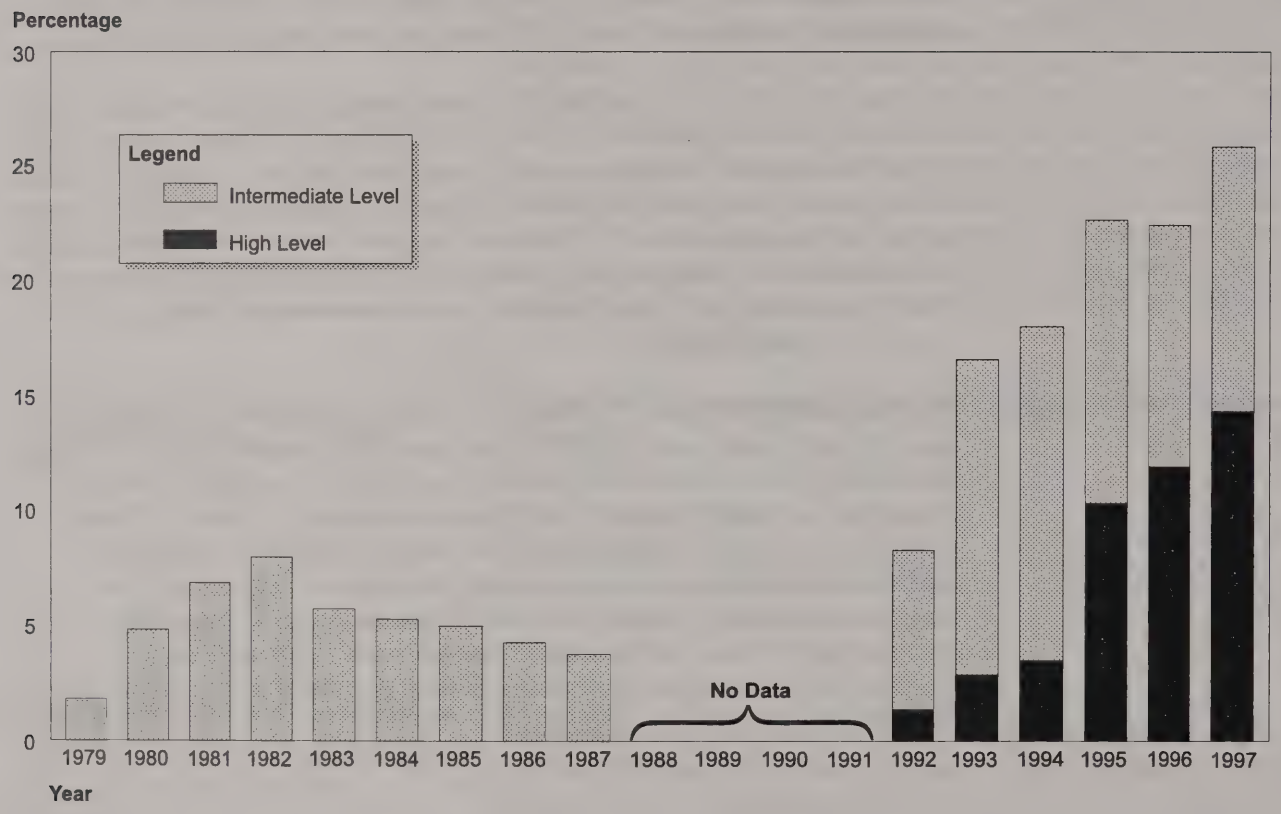
- Bacteria known to be susceptible are becoming resistant. Some bacteria that were once susceptible to certain antibacterials are now resistant to them. For example, *Yersinia pestis*, which causes plague, was universally susceptible to streptomycin, chloramphenicol, and tetracycline. Extensive testing of samples of specific kinds of *Yersinia pestis* collected between 1926 and 1995 in Madagascar had not detected any multidrug resistance. In 1995, however, a multidrug-resistant sample was isolated from a 16-year old boy in Madagascar.[15]

- The proportion of resistant bacteria is increasing in some populations of bacteria. Although existing surveillance systems predominantly monitor the development of resistance in bacteria from sick people in specific countries, and while different geographical areas may exhibit different antibacterial resistance patterns, data overall indicate that a greater proportion of samples being tested are positive for resistance.[16] For example, according to data from CDC, *S. pneumoniae* is becoming increasingly resistant in the United States—that is, an increasing percentage of *S. pneumoniae* samples that are tested in CDC laboratories are resistant to penicillin. (See fig. 3.)

[15]M. Galimand and others, "Multidrug Resistance in *Yersinia pestis* Mediated by a Transferable Plasmid," New England Journal of Medicine, Vol. 337 (1997), pp. 677-80.

[16]Of the studies we identified that examined the resistance patterns of particular populations of bacteria, most found the percentage of resistant bacteria increased over time. However, in some cases, the percentage of bacteria resistant to a specific antibacterial has been relatively stable or declined.

Figure 3: Penicillin Resistance in S. Pneumoniae, 1979 Through 1997



Source: CDC, Sentinel Surveillance Network (1979 through 1994) and Active Bacterial Core Surveillance system (1995 through 1997).

Studies also show that resistance is increasing in other countries. For example, a DOD-funded study on diarrhea-causing bacteria isolated from indigenous persons in Thailand over 15 years shows that ciprofloxacin resistance among *Campylobacter* samples increased from 0 percent before 1991 to 84 percent in 1995.[17] In Iceland, the frequency of penicillin-resistant samples of *S. pneumoniae* rose from 2.3 percent in 1989 to 17 percent in 1992, after detecting penicillin-resistant *S.*

[17]C. W. Hoge and others, "Trends in Antibiotic Resistance Among Diarrheal Pathogens Isolated in Thailand Over 15 Years," Clinical Infectious Diseases, Vol. 26 (1998), pp. 341-45.

pneumoniae for the first time in 1988.[18] In the Netherlands, metronidazole-resistant *Helicobacter pylori* in several Dutch hospitals increased from 7 percent in 1993 to 32 percent in 1996.[19]

In addition to increases in resistance in bacteria that affect people, resistance among bacteria in animals has also been increasing. In Finland, two surveys—carried out in 1988 and 1995—studied the prevalence of inflamed udders in cows and the antibacterial susceptibility of the bacteria that caused them. The investigators found that the proportion of certain types of *S. aureus* resistant to at least one antibacterial drug increased from 37 percent in 1988 to almost 64 percent in 1995.[20] In the Netherlands, a study of *Campylobacter* isolated from poultry products between 1982 and 1989 showed that resistance to quinolones increased from 0 percent to 14 percent.[21]

- Bacteria are becoming resistant to additional antibacterials. Some bacteria that were considered resistant to a particular antibacterial drug have developed resistance to additional antibacterials. For example, in 1989, a multiresistant clone of MRSA was detected in Spain and a multiresistant clone of penicillin-resistant *S. pneumoniae* was detected in Iceland.[22] Similarly, a few cases of MRSA have exhibited an intermediate level of resistance to vancomycin, in addition to their resistance to many other antibacterials.

- Resistant bacteria are spreading. Over the past decade, a number of resistant bacteria are also believed to have spread around the world. Bacteria can be traced by their DNA patterns. Evidence that the DNA patterns of resistant bacteria from geographically diverse places are the same or very similar combined with evidence that resistance in these bacteria have been prevalent in one place and not in the other allows researchers to conclude that a bacterial clone has spread. With

[18]S. Soares and others, "Evidence for the Introduction of a Multiresistant Clone of Serotype 6B *Streptococcus pneumoniae* from Spain to Iceland in the Late 1980s," Journal of Infectious Diseases, Vol. 168 (1993), pp. 158-63.

[19]E. J. van der Wouden and others, "Rapid Increase in the Prevalence of Metronidazole-Resistant *Helicobacter pylori* in the Netherlands," Emerging Infectious Diseases, Vol. 3 (1997), pp. 385-89.

[20]V. Myllys and others, "Bovine Mastitis in Finland in 1988 and 1995—Change in Prevalence and Antimicrobial Resistance," Acta Vet Scand, Vol. 39 (1998), pp. 119-26.

[21]H. P. Endtz and others, "Quinolone Resistance in *Campylobacter* Isolated From Man and Poultry Following the Introduction of Fluoroquinolones in Veterinary Medicine," Journal of Antimicrobial Chemotherapy, Vol. 27 (1991), pp. 199-208.

[22]A clone is genetically and biochemically identical or nearly identical to the parent bacterium. Bacteria are considered clones if there are enough similarities that the probability that the bacteria are different approaches 0.

international travel and trade and the continuous exchange of bacteria among people, animals, and agricultural hosts and environments, resistant bacteria can spread from one country to another. For example, in 1989, a multidrug-resistant MRSA, known as the Iberian clone, was identified during an outbreak in Spain. This clone has spread to hospitals in Portugal, Italy, Scotland, Germany, and Belgium.[23] In 1998, resistant *Shigella* on parsley entered the United States from Mexico, causing two outbreaks of shigellosis in Minnesota.[24]

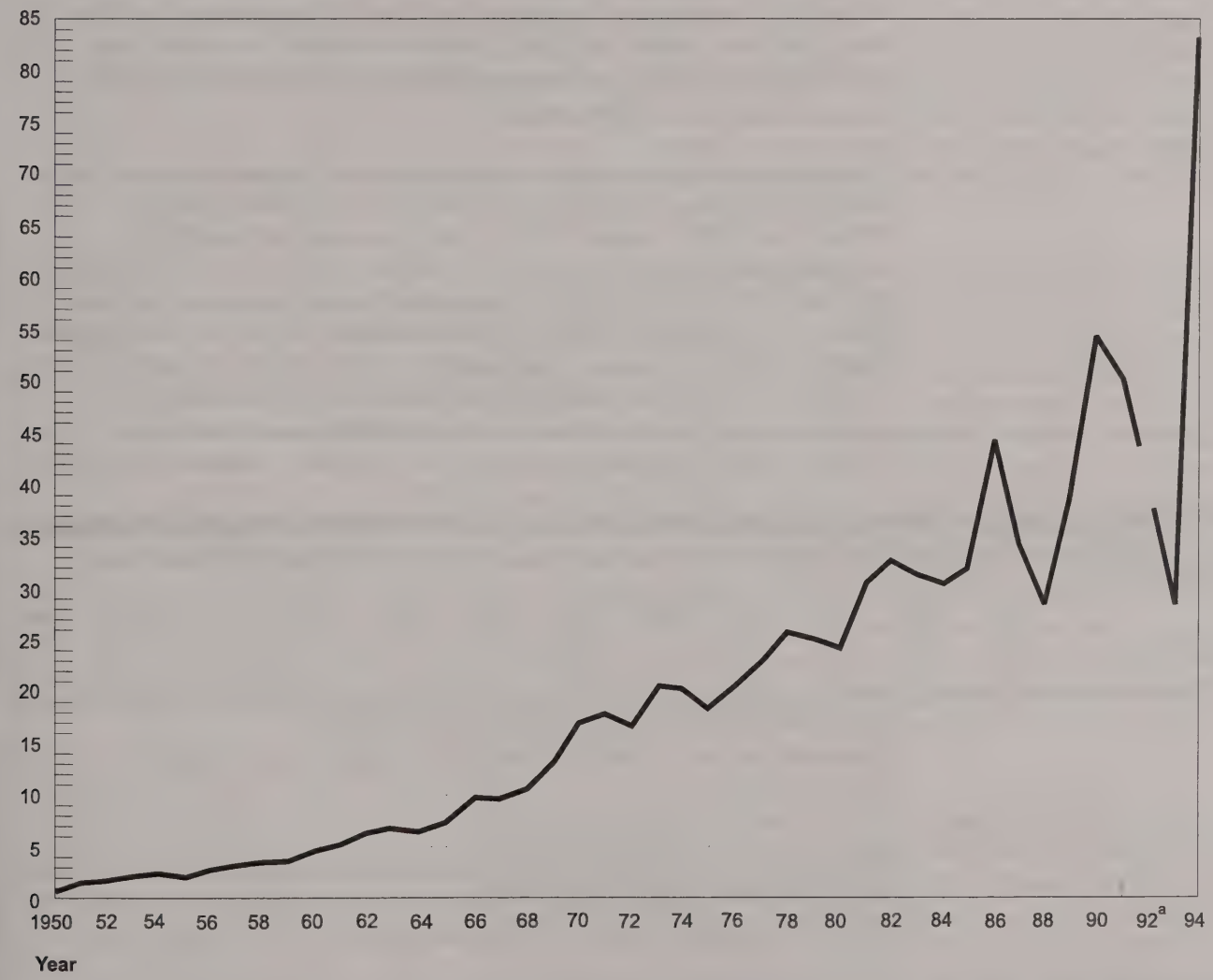
Antibacterials Are Used Widely, but Data Quantifying Use and Residues Are Limited

Antibacterials are used around the world for a number of purposes in various settings, and their use can vary from country to country. Antibacterial drugs are used in both people and animals. Antiseptics and disinfectants are used in hospitals, homes, schools, restaurants, farms, food processing plants, water treatment facilities, and other places. While measures of total antibacterial use in most countries are not available, some data have been published on the total amount of antibacterials produced or sold in the United States. Figure 4 shows the total weight of antibacterial drugs (chemicals, not finished products) produced in the United States from 1950 to 1994.

[23]R. Mato and others, "Spread of the Multiresistant Iberian Clone of Methicillin-Resistant *Staphylococcus aureus* (MRSA) to Italy and Scotland," Microbial Drug Resistance, Vol. 4 (1998), pp. 107-12.

[24]Minnesota Department of Health, unpublished data.

Figure 4: Antibacterial Drug Production, by Year



[a]According to the U.S. International Trade Commission, data on antibiotics were not published in 1992 to avoid disclosure of individual company operations.

Source: Reports of the U.S. International Trade Commission.

According to the Environmental Protection Agency (EPA), a total of 3.3 billion pounds of active ingredients were produced for disinfectants in 1995.[25] We found no estimates of production, sales, or usage of antiseptics. Overall accumulations of antibacterial residue in soil, water, and food are unknown. However, studies have shown that while some antibacterial drugs are rapidly degraded in soil, others remain in their active form indefinitely and that 70 to 80 percent of the drugs administered on fish farms end up in the environment.[26]

- Antibacterial drugs are used to prevent and treat disease in humans. NCHS estimates that from 1980 until 1997, the U.S. antibacterial drug prescription rate remained approximately constant at about 150 prescriptions per 1,000 physician office visits (see table 5). Since 1992, NCHS has collected data on drugs prescribed in hospital emergency and outpatient departments. These data indicate that in 1996, the last year for which all data are available, antibacterial drugs were prescribed 19 million times a year in emergency departments and 8 million times a year in outpatient departments, for a total of 133 million prescriptions for physician office, hospital emergency, and outpatient settings combined.[27]

Table 5: Number (in Millions) and Rate (per 1,000 Visits) of U.S. Antibacterial Drug Prescriptions Written by Office-Based Physicians, 1980, 1981, 1985, and 1989 Through 1997

	1980	1981	1985	1989	1990	1991	1992	1993	1994	1995	1996	1997
Millions of prescriptions	86	87	88	109	111	103	127	109	97	111	106	108
Rate per 1,000 visits	149	149	139	157	158	154	167	152	142	160	145	137

Note: Prescriptions for topical antibacterial drugs are not included.

Source: NCHS, public use data tape documentation and National Ambulatory Medical Care Survey for years shown.

In general, use of antibacterial drugs differs among the countries that have been studied.[28] (Most countries studied are developed countries, but India, South Africa, several Latin American nations, and other less developed

[25]National Service Center for Environmental Publications, "Streamlining Registration of Antimicrobial Pesticides, EPA Progress Report, 1997" (EPA739R97001).

[26]B. Halling-Sorensen and others, "Occurrence, Fate and Effects of Pharmaceutical Substances in the Environment: A Review," Chemosphere, Vol. 36 (1998), pp. 357-93.

[27]Personal communication with L. F. McCaig, NCHS, based in part on L. F. McCaig and J. M. Hughes, "Antimicrobial Drug Prescribing in Ambulatory Care Settings in the United States, 1995-96," presentation at the 1998 convention of the American Public Health Association.

[28]N. F. Col and R. W. O'Connor, "Estimating Worldwide Current Antibiotic Usage: Report of Task Force 1," Reviews of Infectious Diseases, Vol. 9, Supplement 3 (1987), pp. S232-S243.

countries have also been studied.) For example, Japan and Spain have higher rates of cephalosporin sales than do the other countries studied. The Danish Antimicrobial Resistance Monitoring and Research Programme has reported that antibiotic consumption in Denmark's primary care sector declined from 12.8 defined daily doses per 1,000 population in 1994 to 11.3 in 1997.[29] Available reports indicate that the amount of antibacterial drug use per person in some other developed countries, such as Canada, is greater than in the United States.[30] In less developed countries—including Kenya, Bangladesh, and Nigeria—use of some antibacterial drugs tends to be relatively great for the segment of the population who can afford them.[31]

- Antibacterial drugs are used to prevent and treat disease in food animals, pets, and plants. Antibacterial drugs, often the same ones used to prevent and treat disease in humans, are also used in veterinary medicine, fish farming, beekeeping, and agriculture. Veterinarians prescribe antibacterial drugs to treat disease in food animals, such as cattle and swine, and in companion animals, such as dogs and cats. A variety of antibacterial drugs are available without prescription in feed stores and pet stores.[32] Fish farmers who raise fish, such as salmon, catfish, and trout, put antibacterial drugs in water to treat bacterial infection; and beekeepers use antibacterial drugs to prevent and treat bacterial infection in honeybees. Antibacterial drugs are also sprayed on some fruits and vegetables, such as pears and potatoes, as well as on other crops, such as rice and orchids. Chemical industry sources estimated that in 1985, the total weight of antibacterial drugs used to treat and prevent disease in cattle, swine, and poultry in the United States was 13.8 million pounds, but they have not published more recent estimates.

- Antibacterial drugs are used to enhance the growth of food animals and other commercially important animals. Antibacterial drugs are also often administered in the United States as feed additives to enhance growth and increase feed efficiency. As feed additives, they are primarily used for food animals, such as livestock and poultry, but they are also given to other commercially important animals, such as mink. Many antibacterial drugs used to promote growth can be purchased without a prescription.

[29]Eurosurveillance Weekly, Feb. 4, 1999.

[30]Health Protection Branch—Laboratory Centre for Disease Control, "Controlling Antimicrobial Resistance: An Integrated Plan for Canadians," Canada Communicable Disease Report, Vol. 23S7.

[31]For example, I. N. Okeke and others, "Socioeconomic and Behavioral Factors Leading to Acquired Bacterial Resistance to Antibiotics in Developing Countries," Emerging Infectious Diseases, Vol. 5 (1999), pp. 18-27.

[32]S. B. Levy, The Antibiotic Paradox (New York: 1992), p. 175.

Chemical industry sources estimated that in 1985, 4.5 million pounds of antibacterial drugs were used for growth enhancement in cattle, swine, and poultry.

Some other developed countries, such as Canada, also use antibacterial drugs for growth enhancement. However, because of concerns about antibacterial resistance, several countries have banned certain uses of some drugs or particular drugs altogether. For example, Sweden banned all antibacterials for use in animal feed without prescription, and the European Union banned several specific antibacterial feed additives. FDA has efforts under way to determine if similar actions are warranted in this country.[33]

- Antibacterials are applied to various surfaces and environments to inhibit bacterial growth. Antibacterials are also used to disinfect various surfaces and environments in institutional settings, such as hospitals and laboratories; in industrial settings, such as food processing and manufacturing plants; and in environmental health settings, such as water treatment facilities. They are also used as antiseptics to disinfect skin and wounds. The presence of antibacterials in hundreds of consumer products, including soaps, cat litter, cutting boards, and even ballpoint pens, contributes to the public's exposure to them. According to industry sources, almost 700 new antibacterial products were introduced between 1992 and the middle of 1998. Many of these, such as cribs and toys, are for use by children. The American Academy of Pediatrics' Committee on Infectious Diseases is conducting a study of the use and safety of antibacterials in these products and other consumer products, such as hand soaps, that children may come into contact with.

- Antibacterial residues in some foods are monitored, but little is known about other residues. USDA inspects meat and poultry for antibacterial residues and reports on all samples with detectable levels. However, the levels of antibacterials in food that might promote resistance are not known and, therefore, cannot be factored into the current limits. USDA also regularly tests samples of fruits and vegetables for contamination by certain pesticides, such as insecticides, but not for antibacterials. EPA assesses risks of toxicity, but not antibacterial resistance, from residues on fruits and vegetables using data collected by USDA.

[33]See FDA, "A Proposed Framework for Evaluating and Assuring the Human Safety of Microbial Effects of Antimicrobial New Animal Drugs Intended for Use in Food-Producing Animals" (1999).

Residues can also end up in water and soil. Studies in Europe have shown that antibacterials can be found in bodies of water that supply drinking water.[34] However, we know neither the extent to which antibacterials in the environment promote the development of resistance nor how much antibacterial residue ends up in the environment or in food (with the exception of meat) or drinking water.

A Number of Federal and International Agencies Are Collecting Some Information About Antibacterial Resistance

A number of federal agencies and international organizations that receive U.S. funds collect information about the number of resistant infections, the prevalence of resistant bacteria, the cost of treating resistant disease, and the use of antibacterials; some ongoing efforts involve collaboration among several agencies. In addition, nearly two dozen agencies are coordinated under the Committee on International Science, Engineering, and Technology of the White House National Science and Technology Council to address the threat of emerging infectious diseases, which includes drug-resistant infections. Efforts to improve existing data sources and to create new ones are under way at several agencies, and we expect that over the next few years new information will allow better characterization of the public health burden. Several agencies also have data or access to data that, although not originally intended for these purposes, could be used to learn more about the numbers of resistant infections, treatment costs, and usage of antibacterials. Table 6 summarizes the ongoing and newly initiated efforts of agencies to collect information as well as potential data sources.

[34]J. Raloff, "Drugged Waters: Does It Matter That Pharmaceuticals Are Turning Up in Water Supplies?" Science News, Vol. 153 (Mar. 21, 1998), pp. 187-89.

Table 6: Information on the Number of Resistant Infections, Resistant Bacteria, Treatment Costs, and Antibacterial Use Collected by Federal Agencies and Federally Funded Organizations

Ongoing efforts	Newly initiated efforts	Other efforts and potential data sources
Centers for Disease Control and Prevention		
— Through NHDS, estimates drug-resistant infections among hospitalized patients. — Collects from the states reports of every case of TB diagnosed in the United States. — Conducts nationwide surveillance for gonorrhea, and monitors antibacterial resistance in *Neisseria gonorrhoea*. — Through NNIS, reports antibacterial resistance rates for bacteria associated with hospital-acquired infections. — Collects data on resistant bacteria, resistant infections, and antibacterial use in hospitals. — Collects data on use of antibacterial drugs for nonhospitalized patients. — Monitors drug resistance in *S. pneumoniae* from patients with meningitis or infection of the bloodstream.	— Made drug-resistant *S. pneumoniae* nationally reportable in 1995. — Established an international surveillance program involving more than 30 countries in 1997; the program distributes information about emerging resistance.	
Centers for Disease Control and Prevention and U.S. Geological Survey (USGS)		
	CDC is conducting a study on the presence of pharmaceuticals, including antibacterial agents, in confined animal feed operations in Ohio and Iowa and on resistance patterns in the microbial communities of these operations. USGS will be testing the surface water around these facilities for residues.	
Health Care Financing Administration		
		Data on beneficiaries could be used to learn more about resistant infections, antibacterial drug use, and treatment costs.
National Institutes of Health		
	Funds a project to establish the first network and database on antibiotic resistance in bacteria that normally live in close contact with people and animals but generally do not cause disease in their primary hosts.	Intends to award a contract to establish a network for linking multidisciplinary investigators focusing on *S. aureus* and antibacterial resistance and establish a repository for samples of resistant *S. aureus*.

(continued)

Ongoing efforts	Newly initiated efforts	Other efforts and potential data sources
Food and Drug Administration		
Samples domestically produced and imported food, and analyzes them for pesticide residues, including antibacterials, to enforce tolerances set by EPA.	Proposed a framework for ensuring human safety from new and existing animal drugs, which includes collecting more detailed drug sales information than currently collected. Requested marketing data to be reported on a state or regional basis to facilitate monitoring for resistance for some recently approved fluoroquinolone antibacterial products used in cattle and poultry.	— Data that sponsors are required to submit in annual reports on approved human and animal drugs could be used to estimate antibacterial production. — Data purchased from IMS, a private company, could be used to assess the distribution of antibacterial drugs.
Department of Agriculture		
— Samples meat and poultry products and analyzes them for residues, including antibacterials, to enforce tolerances set by EPA. — Through the National Animal Health Monitoring System, periodically assesses the patterns of antibacterial drug use by veterinarians and in animal production.		Developing a program to test for the presence of microorganisms in produce and will make these samples available for research.
Centers for Disease Control and Prevention, Food and Drug Administration, and U.S. Department of Agriculture		
CDC collaborates with FDA and USDA under the National Antimicrobial Resistance Monitoring System—Enteric Bacteria program to monitor resistance in *Salmonella*, *Campylobacter*, and *E. coli* isolated from people and *Salmonella* isolated from animals.	In fiscal year 1998, the National Antimicrobial Resistance Monitoring System—Enteric Bacteria program was expanded to include monitoring for *Campylobacter* and *E. coli* in animals.	
Environmental Protection Agency		
		Data that manufacturers are required to file annually on products registered with the EPA could be used to estimate antibacterial production.
Environmental Protection Agency and U.S. Geological Survey		
	EPA is conducting a study on the presence of pharmaceuticals, including antibacterial agents, in a farm environment and on resistance patterns in the microbial communities of the farm. USGS will be testing the surface and ground water around the farm for residues.	

(continued)

Ongoing efforts	Newly initiated efforts	Other efforts and potential data sources
Department of Defense		
In some developing countries, tropical medical research units collaborate with their host nations to develop networks for surveillance of emerging infections; they also study resistance in bacteria that cause disease acquired in the community.	— Studies on antibacterial resistance in *S. pneumoniae* and *Streptococcus pyogenes* are under way at 13 military sites in the United States. — Collaborating with MRL Pharmaceutical Services, a private company, to develop a system for collecting laboratory data on resistance from military hospitals in the United States.	Data on beneficiaries could be used to learn more about resistant infections, antibacterial drug use, and treatment costs.
Department of Veterans Affairs		
Conducts an annual census in VA facilities nationwide to collect data on infections, including those caused by drug-resistant TB and resistant *Enterococcus* and pneumococcus.	Developed a national surveillance system to track 14 diseases and disease-causing microbes, including several resistant bacteria, in all 171 VA health care facilities.	Data on beneficiaries could be used to learn more about resistant infections, antibacterial drug use, and treatment costs.
U.S. Agency for International Development		
Funds studies in India to determine drug resistance levels of bacteria that cause pneumonia.	— Funds numerous surveillance activities and studies around the world. — Studies antimicrobial drug use in Mozambique, Russia, Peru, Nepal, and Ghana.	
World Health Organization		
— Helps countries establish national surveillance networks to detect resistant bacteria in humans and animals, and provides computer software (WHONET) for collecting and analyzing antimicrobial resistance data. — Coordinates the sharing of data collected from different countries to provide a global database.		

Conclusions

Although many studies have documented cases of infections that are difficult to treat because they are caused by resistant bacteria, the full extent of the problem remains unknown. The development and spread of resistant bacteria worldwide and the widespread use of various antibacterials create the potential for the U.S. public health burden to increase. A number of federal and federally funded agencies are collecting information about different aspects of antibacterial resistance, and some ongoing efforts involve collaboration among agencies. However, there is little information about the extent of the following:

- common diseases that can be caused by resistant bacteria, are acquired in the community, and do not typically result in hospitalization, such as otitis media;
- the development of resistant properties in bacteria that do not normally cause disease but that can pass these properties on to bacteria that do;
- antibacterial use, particularly in animals, and antibacterial residues in places other than food; and
- the development of resistant disease and resistant bacteria and the use of antibacterials globally.

Without improvements in existing data sources and more information in these areas, it is not possible to accurately assess the threat to the U.S. public health posed by resistant bacteria. As you have requested, we will be conducting further studies to (1) explore options for improving existing data sources and developing new ones; (2) identify the factors that contribute to the development and spread of antimicrobial resistance; and (3) consider alternatives for addressing the problem.

Agency Comments

We provided a draft of this report to CDC, EPA, FDA, the Health Care Financing Administration (HCFA), the National Institutes of Health (NIH), USDA, and to experts at other agencies. In general, the agencies agreed with our findings. The Department of Health and Human Services (HHS) concurred with the information and conclusions presented in the report but "is concerned that the draft report . . . is not as unequivocal as it could be in stating the gravity of the problem." While we recognize that resistant bacteria threaten public health, we concluded that currently available data on the public health and economic consequences of antibacterial resistance are too limited for us to characterize the full extent of the problem. The agencies also provided technical or clarifying comments, which we incorporated as appropriate.

As agreed with your office, unless you publicly announce its contents earlier, we plan no further distribution of this report until 30 days from the date of this letter. At that time, we will send copies to the Honorable Donna E. Shalala, Secretary of HHS; the Honorable Jeffrey Koplan, Director of CDC; the Honorable Jane Henney, Commissioner of FDA; the Honorable Nancy-Ann Min DeParle, Administrator of HCFA; the Honorable Harold Varmus, Director of NIH; the Honorable Carole Browner, Administrator of EPA; the Honorable Dan Glickman, Secretary of USDA; and other interested parties. We will make copies available to others upon request.

If you or your staff have any questions, please contact me at (202) 512-7114 or Cynthia Bascetta, Associate Director, at (202) 512-7101. Other major contributors to this report are listed in appendix V.

Sincerely yours,

William J. Scanlon

William J. Scanlon
Director, Health Financing
and Public Health Issues

Contents

Figures

Abbreviations

CDC	Centers for Disease Control and Prevention
DNA	deoxyribonucleic acid
DOD	Department of Defense
EPA	Environmental Protection Agency
FDA	Food and Drug Administration
GISP	Gonococcal Isolate Surveillance Project
HCFA	Health Care Financing Administration
HHS	Department of Health and Human Services
ICARE	Intensive Care Antimicrobial Resistance Epidemiology
MRSA	methicillin-resistant *Staphylococcus aureus*
MSSA	methicillin-sensitive *Staphylococcus aureus*
NCHS	National Center for Health Statistics
NHDS	National Hospital Discharge Survey
NIH	National Institutes of Health
NNIS	National Nosocomial Infections Surveillance
OTA	Office of Technology Assessment
TB	tuberculosis
USDA	U.S. Department of Agriculture
USGS	U.S. Geological Survey
VISA	vancomycin intermediate-resistant *Staphylococcus aureus*
VRE	vancomycin-resistant *Enterococcus*

Scope and Methodology

Although resistance has been observed in many kinds of microbes—including bacteria, viruses, parasites, and fungi—the scope of our work was limited to bacteria. The scope of our work was also limited to resistance to chemical antibacterials, although bacteria can be resistant to other phenomena, such as radiation or extremes of temperature. We focused on estimating the numbers of cases of illness and death caused by resistant bacteria and on estimating the costs of treating resistant infections; we did not, however, attempt to capture all aspects of the public health burden. Our focus is on what is known about the burden in the United States resulting from resistance, but we considered global developments in assessing the potential future burden. The federal efforts we examined include international activities assisted by federal funds. We did not attempt to examine all federal efforts related to antimicrobial resistance, but focused on efforts to collect and provide information on cases of resistant infections, resistance in bacteria, use of antibacterials, and the cost of treating resistant diseases.

To conduct our work, we reviewed scientific and medical literature; identified sources of data; and consulted experts in government, including those at the Centers for Disease Control and Prevention (CDC), the National Institutes of Health, the Food and Drug Administration (FDA), the Health Care Financing Administration, the Agency for Health Care Policy and Research, the Environmental Protection Agency (EPA), the U.S. Department of Agriculture (USDA), the Department of Veterans Affairs, the Department of Defense (DOD), the U.S. Agency for International Development, and the World Health Organization. We also consulted experts in academia and private industry. We did not conduct our own statistical analyses to estimate the public health burden or independently verify the databases or analyses of others. We conducted our work between June 1998 and April 1999 in accordance with generally accepted government auditing standards.

Resistant Bacteria

Bacteria are single-celled microbes that exist almost everywhere—in water, soil, plants, animals, and humans. They can transfer between hosts and be carried across borders through travel and trade. They typically live as members of communities of different organisms, such as fungi and algae. Bacteria and other microbes that normally occupy a particular niche are referred to collectively as the microflora of that niche. These organisms compete with each other for nutrients, oxygen, and space. Those that do not compete successfully are likely to be eliminated from the habitat. A foreign microbe usually has difficulty establishing itself in a stable community for this reason. Preventing foreign microbes from colonizing a site of the body is one of the most important benefits provided by normal microflora to their hosts. If an environmental disturbance, such as the introduction of an antibacterial drug, changes the balance of the community by killing the microflora susceptible to the effects of the drug, resistant foreign bacteria would have the opportunity to grow in the community and possibly cause disease.

Most bacteria are harmless, and some are even useful to their hosts. For example, some bacteria normally found in the digestive tracts of animals and people help their hosts to digest nutrients that are important sources of energy, proteins, and vitamins. While most bacteria are benign, others are capable of causing disease. For example, *E. coli* O157:H7—which can be found in the feces of healthy cattle and can transfer to people through contaminated undercooked ground meat or unpasteurized milk products and juices—produces a toxin that causes severe stomach and bowel disorders and can result in failure of the blood-clotting system, acute kidney failure, and even death. The same bacteria that can cause disease in an individual may also be part of that individual's normal microflora. *Enterococcus faecalis* is part of the microflora of the human intestine and, until recently, were generally considered harmless. These bacteria are harmless while they remain in the intestine, but when they enter the bloodstream through a wound or as a complication of invasive medical procedures, they can cause a blood infection.

Like other living things, as bacteria grow and multiply, they also evolve and adapt to changes in their surroundings, which includes the introduction of antibacterial drugs into their environment. Some bacteria may have mutations in their DNA that allow them to avoid the effects of the antibacterial and outgrow the other bacteria in the population. They may also acquire plasmids—small, circular, self-replicating DNA molecules in addition to their own chromosomes—carrying genes that confer resistance to specific antibacterials. Like the bacteria that move freely between hosts

and environments, these plasmids can be transferred from one bacterium to another within a species and sometimes between certain species of bacteria.

Methods of Assessing Antibacterial Resistance Differ

Laboratories may use different types of antibacterial susceptibility tests, which can produce varying results. Discrepancies in test results can have therapeutic consequences if testing indicates that a particular type of bacteria will be susceptible to a specific antibacterial while, in practice, the drug fails to eliminate the infection. In general, however, the drug of choice usually can treat the susceptible strains successfully. Even in some instances where a susceptible organism is not killed, it is not necessarily a failure of the test to predict clinical susceptibility. Many other factors, including the site of the infection and the duration of treatment, can make a susceptible bacteria appear clinically resistant.

In addition to the use of different tests to determine resistance, countries currently follow a number of laboratory standards for interpreting the test results. One study found that Scandinavia, Germany, the Netherlands, the United Kingdom, and France all follow different standards. Spain and some other southern European countries are mainly under the influence of the standards followed in the United States. Therefore, the breakpoints—where lines are drawn to distinguish between susceptible and intermediate resistance or intermediate resistance and high resistance—can differ among various countries around the world, although data sets should be comparable at laboratory facilities that use the same method and standards over time.

Resistant Bacteria Are Found Around the World in People and Animals

In addition to determining the clinical effect of antibacterials against bacteria, antibacterial susceptibility tests are used to detect the emergence and spread of resistance. While there is a lack of routine testing and systematic data collection on antibacterial resistance globally, existing data on resistant bacteria in particular hosts and from specific geographic locations show that a variety of resistant bacteria can be found in people and animals in many different areas around the world. The level of resistance, however, can vary among settings and geographic areas. For example, while vancomycin-resistant *Enterococcus* (VRE) occurs in both hospitalized and nonhospitalized individuals in Europe, a study of healthy individuals; hospitalized patients; and farm animals in Houston, Texas, indicates that in the greater Houston metropolitan area, VRE is rare or

nonexistent among nonhospitalized people.[35] Similarly, investigators from the SENTRY[36] Antimicrobial Surveillance Program found that the proportion of VRE isolated from the bloodstream of patients in the United States during a 6-month period was about 18 percent, while none of the *Enterococcus* samples from Canada were vancomycin resistant.[37]

Much of the testing and surveillance are also conducted predominantly on patient samples, so the data do not reflect the levels of resistance for bacteria in all other environments. These efforts, however, provide some information about where resistant bacteria can be found. For example, in Portugal, the prevalence of methicillin-resistant *S. aureus* has remained high at 50 to 65 percent in Portuguese hospitals between 1992 and 1995.[38] In the United States, the National Antimicrobial Resistance Monitoring System—Enteric Bacteria,[39] which tests *Salmonella* samples isolated from people, found that 21.7 percent of the *Salmonella* samples were resistant to streptomycin, while all were susceptible to ciprofloxacin. A DOD medical research unit in Peru tested disease-causing bacteria that affect the intestine and found that 38 percent of the *Campylobacter* samples were resistant to ciprofloxacin; 52 percent of the *Shigella* samples, 99 percent of the *Salmonella* samples, and 85 percent of the *E. coli* samples were resistant to azithromycin; and all *Vibrio cholerae* samples were sensitive to quinolones.[40] CDC investigators tested *Shigella* from patients in outpatient clinics in Burundi and found that 100 percent were multidrug resistant.[41]

Testing of bacteria that colonize animals has also shown varying levels of resistance among different species of animals. For example, the April 1998

[35]T. M. Coque and others, "Vancomycin-Resistant Enterococci From Nosocomial, Community, and Animal Sources in the United States," Antimicrobial Agents and Chemotherapy, Vol. 40 (1996), pp. 2605-9.

[36]SENTRY is a global surveillance program designed to detect trends in antimicrobial resistance. It is sponsored by Bristol-Myers Squibb Co., and over 72 laboratories from four continents currently participate.

[37]M. A. Pfaller and others, "Bacterial Pathogens Isolated From Patients With Bloodstream Infection: Frequencies of Occurrence and Antimicrobial Susceptibility Patterns From the SENTRY Antimicrobial Surveillance Program (United States and Canada, 1997)," Antimicrobial Agents and Chemotherapy, Vol. 42 (1998), pp. 1762-70.

[38]I. S. Sanches and others, "Multidrug-Resistant Iberian Epidemic Clone of Methicillin-Resistant *Staphylococcus aureus* Endemic in a Hospital in Northern Portugal," Microbial Drug Resistance, Vol. 1 (1995), pp. 299-306.

[39]The program was established by USDA, FDA, and CDC, with participation from local and state health departments.

[40]DOD, unpublished data.

[41]Personal communication with Robert V. Tauxe, Chief, Foodborne and Diarrheal Diseases Branch, Division of Bacterial and Mycotic Diseases, National Center for Infectious Diseases, CDC.

Report of the National Antimicrobial Resistance Monitoring System—Enteric Bacteria shows that for samples of *Salmonella* from sick animals, 75 percent of swine samples, 69 percent of turkey samples, 37 percent of cattle samples, 23 percent of horse samples, and 13 percent of chicken samples tested positive for resistance to tetracycline. The same samples were all susceptible to ciprofloxacin. Percentages were lower when samples from healthy animals are included. In the Netherlands, a study of bacterial samples taken from 23 dogs and 24 cats at an urban general veterinary practice showed that 48 percent of the dogs and 16 percent of the cats were colonized with VRE. This incidence of VRE in pets exceeded that among the people living in the same geographic area, which was 2 to 3 percent.[42] In an effort to establish a baseline of resistance to therapeutic antibacterial agents among bacteria from food animals in Denmark, the Danish Integrated Antimicrobial Resistance Monitoring Programme tested indicator bacteria (such as *E. coli* and *Enterococcus faecalis*), zoonotic bacteria (such as *Campylobacter jejuni*), and animal pathogens (such as *Actinobacillus pleuropneumoniae*).[43] The results from their study showed that resistance to all of the antibacterial agents can be found, although there were significant differences in the occurrence of resistance among different bacterial species.[44]

Resistance Genes Can Transfer to Different Kinds of Bacteria

In addition to testing for resistance in bacterial samples from people and animals, some laboratories around the world are examining bacteria for the presence and transfer of specific resistance genes. Genetic exchanges do not occur indiscriminately within bacterial populations. Barriers to gene transfers—such as destruction of genes considered foreign by the host bacterium—can reduce the likelihood of successful transfer events. Nevertheless, data on the transfer of resistance genes between different kinds of bacteria can provide some information about where these genes may have been acquired and how they spread to different environments and geographic locations. A number of studies examining the DNA sequences of resistance genes show similarities among these genes in evolutionarily diverse bacteria, suggesting that some transfers have been occurring naturally between certain kinds of bacteria. For example, plasmids carrying resistance genes that were found in bacteria isolated

[42]A. van Belkum and others, "Vancomycin-Resistant Enterococci in Cats and Dogs," Lancet, Vol. 348 (1996), pp. 1038-39.

[43]Indicator bacteria are bacteria that easily acquire resistance and are found in different animal species; zoonotic bacteria are bacteria that can be transmitted between animals and humans.

[44]F. M. Aarestrup and others, "Resistance to Antimicrobial Agents Used for Animal Therapy in Pathogenic, Zoonotic, and Indicator Bacteria Isolated From Different Food Animals in Denmark: A Baseline Study for the Danish Integrated Antimicrobial Resistance Monitoring Programme (DANMAP)," APMIS, Vol. 106 (1998), pp. 745-70.

from patients suffering from multiresistant *Shigella* infections on a Hopi Indian reservation in New Mexico appeared to come from multiresistant *E. coli*.[45]

Most studies on the exchange of resistance genes among different bacterial species have been conducted under laboratory-defined conditions. While some of these studies suggest that resistance genes can be transferred between certain species and even across bacterial genera,[46] evidence of gene transfer in the laboratory demonstrates only that the transfer is possible, not whether that transfer will occur in nature. Many studies are also focused on bacteria isolated from patients. Even where there is surveillance for resistance, the surveillance systems tend to be limited to the monitoring of specific bacterial diseases, such as TB and gonorrhea, or disease-causing bacteria, such as *S. pneumoniae*. Therefore, less information is available on the prevalence of resistant genes in bacteria isolated from healthy people and that do not generally harm their primary host. Nevertheless, there is some evidence that resistance genes in these bacteria may play a role in the spread of antibacterial resistance.

For example, an interspecies gene transfer appears to have occurred in the United States in 1979, when a multiresistant plasmid was identified in Kentucky in hospital patients and personnel infected with *S. aureus*. A year earlier, a like plasmid was isolated from *Staphylococcus epidermidis* on hospital patients, which suggests that the same plasmid was transferred from these bacteria to *S. aureus*.[47] Bacteria from different body sites of one host may also exchange genes. For example, studies on tetracycline-resistant *Bacteroides* and *Prevotella* suggest that genetic exchange may occur between bacteria from the gastrointestinal tract and bacteria found in the mouth.[48] In a study of gene transfers in simulated natural microenvironments, transfers were observed between bacteria

[45]R. V. Tauxe and others, "Interspecies Gene Transfer In Vivo Producing an Outbreak of Multiply Resistant Shigellosis," Journal of Infectious Diseases, Vol. 160 (1989), pp. 1067-70.

[46]Like other organisms, each bacterium is a member of an order, a family, a genus, and a species. A species can be further subdivided into strains of bacteria. *Staphylococcus* and *Escherichia* are genera, while *aureus* is a species of *Staphylococcus* and *coli* is a species of *Escherichia*.

[47]*Staphylococcus epidermidis* and *S. aureus* are bacteria that normally live on the skin and mucous membranes of humans. M. L. Cohen and others, "Common R-plasmids in *Staphylococcus aureus* and *Staphylococcus epidermidis* During a Nosocomial *Staphylococcus aureus* Outbreak," Antimicrobial Agents and Chemotherapy, Vol. 21 (1982), pp. 210-15.

[48]N. B. Shoemaker and others, "Evidence for Natural Transfer of a Tetracycline Resistance Gene Between Bacteria From the Human Colon and Bacteria From the Bovine Rumen," Applied and Environmental Microbiology, Vol. 58 (1992), pp. 1313-20; and D. G. Guiney and K. Bouie, "Detection of Conjugal Transfer Systems in Oral, Black-Pigmented *Bacteroides* spp.," Journal of Bacteriology, Vol. 172 (1990), pp. 495-97.

from different hosts—cow *E. coli* to fish *Aeromonas salmonicida* in marine water, cow *E. coli* to human *E. coli* on a hand towel treated with cow's milk, and pig *E. coli* to human *E. coli* on a cutting board.[49] Resistant bacteria, therefore, are not only a potential cause of disease but also may be a source of resistance genes that can be transferred to benign and disease-causing bacteria of diverse origins.

[49]H. Kruse and H. Sorum, "Transfer of Multiple Drug Resistance Plasmids between Bacteria of Diverse Origins in Natural Microenvironments," Applied and Environmental Microbiology, Vol. 60 (1994), pp. 4015-21.

Antibacterial Uses

Antibacterials are recognized as major contributors in the development of antibacterial resistance. There are many kinds of antibacterials, varying in how they are used and in the agencies that have jurisdiction over them. Both the amount and usefulness of information on the quantities of antibacterials used are limited.

How They Are Used

Pharmacologists and physicians recognize several classes of antibacterial drugs that can differ in their mechanisms of action, killing, or inhibiting the growth of bacteria in varied ways. Therefore, for a given kind of bacterial infection in a human, a particular antibacterial drug will usually be the drug of choice—or first-line treatment—with one or more second-line treatments usually available if the drug of choice cannot be used or fails to stop the infection. The therapeutic uses of antibacterial drugs are well known, but their preventive role may be less appreciated. About half of all antibacterial drugs used on surgical patients in large hospitals are used to prevent possible infections. The percentage of the antibacterial drugs prescribed outside the hospital for preventive as opposed to therapeutic purposes is unknown. Antibacterial drugs are also used to prevent and treat disease in plants and animals and to promote growth in food animals.

Antiseptics and disinfectants are also used for a variety of purposes. For example, phenolic compounds, such as triclosan, are used in hand soaps and toothpastes; nitrogen heterocycles are used as preservatives in cosmetics and other products; sulfur compounds are used as food preservatives; and gaseous sterilants are often used in hospitals on equipment that cannot be sterilized at high temperatures. Other commonly used antiseptics and disinfectants include chlorine; ethyl alcohol; formaldehyde; hydrogen peroxide; and metal compounds, such as mercurochrome.

Jurisdiction Over Antibacterials

In the United States, all drugs introduced into interstate commerce, including antibacterials used in human and animal medicine, are subject to FDA approval. All pesticides, including antibacterial drugs used on plants, must be registered with EPA. Most antibacterial drugs for human use require a prescription, but a few that are topically applied are available without a prescription. In some other countries, however, antibacterial drugs for humans that act systemically may be available without a prescription. Some antibacterial drugs for animal use require a

prescription, but some are available without a prescription in pet stores and feed stores. FDA determines whether a prescription is required.

FDA also has jurisdiction over other antibacterials that come in direct contact with people, such as antiseptic hand soaps. EPA has jurisdiction over those that do not, such as detergents, antibacterials used to impregnate cutting boards, and gases used to sterilize equipment. Some products do not neatly fall under a single agency. FDA and EPA are attempting to clarify some of the "gray area" between their respective jurisdictions, with special attention to those products that may come in contact with food.

FDA requires manufacturers to maintain distribution records, including quantity, for drug products administered to humans and animals. These data are required to be reported annually to FDA, but FDA does not compile them to yield estimates of aggregate antibacterial drug usage. FDA's Center for Drug Evaluation and Research, which handles human drugs, expects that when it moves to a planned new computer system and requires certain changes to the way marketing information is submitted, preparation of such estimates will be easier. FDA's Center for Veterinary Medicine, which handles animal drugs, has initiated some special postapproval programs to monitor the use of fluoroquinolone antibacterials in poultry and cattle. The center is also changing the way marketing information is submitted and enhancing its database to facilitate development of information on antibacterial usage generally. EPA requires producers of pesticides, some of which are antibacterials, to report annually on the amounts of pesticide produced, distributed, and sold during the past year. It has provided usage estimates for some kinds of antibacterial pesticides.[50]

Quantities Used

We found some data on usage, but different sources of data capture use in different ways, such as weight produced, weight sold, amount sold in dollars, number of prescriptions, and number of doses. The U.S. International Trade Commission published annually the weights of all antibiotics (chemicals, not finished products) produced in the country from 1950 to 1994. These figures do not necessarily indicate the amount of antibiotics used domestically, as some produced here may have been exported, and some produced elsewhere may have been imported. Although there is some indication of an increase in production over the years, the figures sometimes fluctuate for unknown reasons. For example,

[50]"Streamlining Registration of Antimicrobial Pesticides: 1997 EPA Progress Report."

from 1993 to 1994, the weight almost tripled, from nearly 29 million pounds to 83 million pounds. Such fluctuations suggest that these figures be interpreted with caution. Moreover, these figures reveal nothing about how much of each antibacterial drug is used in each setting at a given point in time and geographic location.

Settings in human medicine using antibacterial drugs are ambulatory settings (physicians' offices, emergency rooms, and outpatient clinics) and inpatient settings (hospital wards and rooms). The National Center for Health Statistics (NCHS) estimates the use of commonly prescribed drugs in ambulatory settings for the country as a whole and for large geographic regions. Since 1980, NCHS has periodically collected data on drugs prescribed in physicians' offices as part of its series of National Ambulatory Medical Care Surveys. Since 1992, NCHS has also collected data on drugs prescribed in hospital emergency and outpatient departments as part of the National Hospital Ambulatory Medical Care Survey.

While NCHS does not survey hospitals to obtain national estimates of antibacterial drug use in inpatients, such estimates can be derived by combining NCHS' estimates of the average inpatient population and data from CDC's Intensive Care Antimicrobial Resistance Epidemiology (ICARE) project, which obtains usage rates aggregated over most antibacterial drugs from its 41 participating hospitals. When rates from the ICARE survey are projected to the entire population of U.S. hospitals, it is estimated that about 82 million daily doses of antibacterial drugs were administered in hospitals in 1995. This figure is an underestimate to the extent that the survey does not include all antibacterial drugs, and it is an overestimate to the extent that the hospitals in ICARE's sample probably tend to use more antibiotics than does the average hospital.

Records from pharmaceutical companies and large health care insurers or health plans may also contain information on drug use in ambulatory care but are not generally available to the public. FDA has, for the purpose of studying adverse drug reactions, obtained usage data from IMS Health, a company that collects them and sells them to firms in the pharmaceutical industry and to other customers. FDA, in collaboration with GAO, analyzed these data to estimate ambulatory use. The resulting estimates tend to be higher than those derived from the NCHS data and, unlike the NCHS data, decline over the years from 1993 to 1997. The reasons for these discrepancies include methodological differences in data collection and analysis.

Other potential sources for human usage data include agencies that provide health care, such as DOD, the Department of Veterans Affairs, the Health Care Financing Administration, and various private managed care and health insurance plans. These sources may not collect such data from all whom they serve or be able to provide nationally representative usage estimates, but the available data could be used to assess use in defined segments of the population.

Companies that manufacture drugs for animals and plants do not usually publish production data, but the Animal Health Institute, an industry association, has released data on sales in dollars of antibacterials used in animals. In 1991, the last year for which the data were released, the amounts were $382 million for feed additives and $369 million for pharmaceuticals. Other data from the same source indicate that in the early 1980s, the total annual sales by weight for use in livestock and poultry varied between 10 million and 12 million pounds.

Cost of Treating Resistant Infections

Most cost-of-treatment studies are limited to infections acquired in hospitals—often in only one specific site of infection—and to a small number of cases in a single hospital. In addition, these studies generally use only hospital costs. The few exceptions that we identified are summarized below.

A 1987 study reviewed 185 reports of investigations of bacterial infections in sporadic cases and outbreaks in hospital and community settings during the 1970s.[51] According to the authors of the study, deaths, the likelihood of hospitalizations, and length of hospital stays were "usually at least twice as great" for patients infected with drug-resistant bacteria as for those infected with drug-susceptible bacteria. The study is limited by the small number of cases in any single outbreak report and by the small number of comparisons with case data on both antimicrobial susceptibility or resistance and length of hospital stay.

A 1989 study developed an economic model to determine the potential magnitude of the problem posed by drug-resistant bacteria and the data needed to provide a more definitive statement about its extent.[52] The author concluded that the annual cost resulting from the reduced effectiveness of antimicrobial drugs "appears to be at least $100 million and may exceed $30 billion." The 300-fold range comes from the author's use in the economic model of differing estimates of (1) the occurrence of resistant disease and its case fatality rates, (2) antibiotic use, and (3) the value of human life.

A 1995 report by the now defunct Office of Technology Assessment (OTA)[53] applied the 1987 twofold length of hospital stays to the charges for extra days of hospitalization in three hospitals in 1975 resulting from five kinds of hospital-acquired infections caused by six bacteria[54]—the number of which were first extrapolated from a group of sentinel hospitals to all U.S. hospitals[55]—and then reduced to the fraction that were drug-resistant in

[51]Holmberg and others,"Health and Economic Impacts of Antimicrobial Resistance."

[52]C. E. Phelps, "Bug/Drug Resistance," Medical Care, Vol. 27, No. 2 (1989), pp. 194-203.

[53]OTA, Impacts of Antibiotic-Resistant Bacteria (OTA-H-629, Sept. 1995).

[54]R. W. Haley and others, "Extra Charges and Prolongation of Stay Attributable to Nosocomial Infections: A Prospective Interhospital Comparison," American Journal of Medicine, Vol. 70, No. 1 (1981), pp. 51-58.

[55]R. W. Haley and others, "The Nationwide Nosocomial Infection Rate: A New Need for Vital Statistics," American Journal of Epidemiology, Vol. 121, No. 2 (1985), pp. 159-67.

hospitals in CDC's National Nosocomial Infections Surveillance system.[56] Using an estimate of $661 million for the extra charges for hospitalization in 1992 for these proportions of the five kinds of hospital-acquired bacterial infections, OTA doubled the costs and concluded that the extra hospital costs associated with five drug-resistant, hospital-acquired bacterial infections is $1.3 billion per year.

[56]W. J. Martone and others, "Incidence and Nature of Endemic and Epidemic Nosocomial Infections," in Hospital Infections, 3rd ed., J. V. Bennett and P. S. Brachman, eds. (Boston, Mass.: Little, Brown, and Co., 1992), pp. 577-96.

Major Contributors to This Report

The major contributors to this report are Angela Choy, Donald Keller, Michele Orza, and Richard C. Weston.

Others who contributed include Claude Adrien, George Bogart, Natalie Herzog, Lynne Holloway, Erin Lansburgh, Stuart Ryba, and Karen Sloan.

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